Remarks

Amendment in the specification

Applicants have corrected a typographical error in the spelling of 2-pyrrolidone and N-methyl-2-pyrrolidone. Support for the amendment can be found in the enclosed pages of the Merck Index (1983) which contains the correct spelling and structure for 2-pyrrolidone.

Information Disclosure Statement

Please note that information disclosure statements have been filed to cite art from corresponding foreign applications.

Amendments to the claims

The claims have been amended to be specific to a hydroalcoholic carrier comprising a transdermal penetration enhancer. Support is found in at least claim 5 as originally filed and page 8, lines 10-11. Support for amended claim 5 is found in the examples, specifically formulation #2 in example 1.

Rejection Under 35 U.S.C. § 103

Claims 1-5, 7 and 8 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,993,856 to Ragavan. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The starting point for any such analysis must be the Supreme Court's decision in *KSR*, which refocuses the determination of whether a claimed invention is obvious back to the process

the Court had defined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). There, the Court had held that the obviousness determination should address four factors, all of which must be considered, though not in any prescribed order: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any secondary considerations suggesting nonobviousness, such as commercial success, failure of others, and long felt but unmet need. *Id.* The Court cautioned that the fact finder should be careful about reading the teachings of the invention at issue into the prior art, to avoid applying inappropriate hindsight, *ex post* reasoning. *Id.* at 36.

Analysis

(a) The scope of the prior art

U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1")

Ragavan 1 discloses formulations for topical or local delivery on reproductive organs to achieve relatively highly high blood levels in the regions to be treated in the substantial absence of systemic levels which might cause side effects. Ravagan 1 does not disclose a hydroalcoholic carrier, much less that a transdermal penetration enhancer should be included in the formulation. The formulations of Ragavan 1 are intended for delivery across the mucosal membranes, which does not present the difficulty associated with transport through the skin. The mere disclosure of compounds that can be used as penetration enhancers in Ragavan 1 does not teach which combination of the disclosed elements would be effective in delivering the drug across the stratum corneum.

U.S. Patent No. 5,614,212 to D'Angelo (D'Angelo)

D'Angelo discloses transdermal administration of high molecular weight drugs using a permeation enhancer.

(b) Ascertaining differences between the prior art and the claims

As admitted the by the Examiner, Ravagan 1 does not illustrate the danazol forumulation formulated with a hydroalcoholic carrier including a transdermal penetration enhancer, the formulation providing relief from disease or disorders of the breast and the property of the carrier ***capable of delivering the drug to the breast tissue*** and to promote delivery of the drug across the stratum corneum with low serum drug levels compared to the systemic administration of the drug (Office Action mailed May 1, 2009, page 7, second paragraph). The cited art does not teach *which* formulations are capable delivering the drug across the stratum corneum, as required by claim 1.

(c) Secondary consideration of obviousness

Applicants refer to example 1 of the application and the declaration under C.F.R. 1.132 submitted with this amendment and response, both of which clearly demonstrate statistically significant unexpected results. As described in statements 5-9, experiments were designed to test the skin permeability of an intravaginal formulation such as those disclosed in Ragavan 1. The data presented in Exhibit 2, page 6, Table 3, indicate that this formulation was **ineffective** at penetrating the skin. This experiment demonstrates that the formulations of Ragavan 1 do not penetrate the stratum corneum.

The experiment described in Example 1 of the specification, and again in paragraphs 10-12, of the Declaration under C.F.R. 1.132, demonstrates that a hydroalcoholic gel formulation including a transdermal penetration enhancer is more effective in delivering drug across the stratum corneum than either (1) a non-hydroalcoholic formulation or (2) an alcoholic formulation not including a penetration enhancer, (Exhibit 3, page 4, Figure 1 and page 5, Table 3). Although the formulation containing alcohol was effective in penetrating the skin, the flux was lower than when the formulation included a transdermal penetration enhancer (0.055 $\mu g/cm^2/hr$) (Statement 13, and Exhibit 3, page 5, Table 2).

The penetration enhancer 2-pyrrolidone was added to various formulation to improve the rate of flux, and formulations were tested for their ability to improve flux across the stratum corneum. 15% pyrrolidone did not enhance danazol flux (0.004 $\mu g/cm^2/hr$) in the PEG ointment (i.e., a non-alcoholic carrier). In contrast, 15% pyrrolidone in the presence of 47% alcohol enhanced the danazol flux rate (0.127 $\mu g/cm^2/hr$) of hydroalcoholic gel # 2, a rate of flux twice that seen with oleyl alcohol alone (Exhibit 5, page 5, Table 2). These findings were unexpected.

Neither Polyvinyl pyrrylidone (PVP) in topical drug formulations as described by Ragavan, nor PVP as a penetration enhancer as described by D'Angelo, lead one to the combination with a hydroalcoholic carrier.

Rebuttal evidence may include evidence of "secondary considerations," such as commercial success, long felt but unsolved needs, failure of others, and/or evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior

art. Applicants have shown with the evidence presented in the example in the application and the declaration under C.F.R. 1.132, that the claimed formulation including both a hydroalcoholic gel carrier and a penetration enhancer is significantly more effective in delivering drug across the stratum corneum. Applicants have shown that neither an intravaginal formulation, such as those described in Ravagan 1, nor a non-alcoholic PEG ointment were effective in penetrating the skin. It is the *combination* of the hydroalcoholic gel *and* a penetration enhancer that solublizes the drug and enhances flux of the drug through the skin. These results were unexpected. It would not have been obvious based on the disclosure of Ravagan 1 to choose the formulation of the instant application.

Double Patenting Rejection

U.S. Patent No. 5,993,856 to Ragavan, et al. ("Ragavan 1")

Claims 1-3, 7 and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 and 31-33 of U.S. Patent No. 5,993,856 to Ragavan ("Ragavan 1"). This rejection is improper based on a comparison of the pending claims 1-5, 7 and 8, with claims 1-15 and 31-33 of the Ragavan for the same reason that Ragavan neither discloses nor makes obvious the claimed subject matter.

Independent claim 1 of Ragavan 1 defines micro- or nano-particulate drug formulation for local or regional topical administration of an effective amount to provide relief from symptoms associated with a disease or disorder in a region in patients in need thereof, wherein

the effective amount is less than the effective amount when the drug is administered systemically.

Independent claim 31 defines a composition for treating endometriosis comprising danazole in a form promoting quick uptake into the blood stream when applied to the **mucosal** membranes of the female reproductive tract, wherein danazole is in a form delivering an effective amount to decrease the discomfort of endometriosis which is less than the effective amount when the drug is administered systemically.

The claims of Ravagan 1 do not teach the carrier of the instant application. As amended, claim 1 of the instant application recites a hydroalcoholic gel in combination with a transdermal penetration enhancer. None of the claims of Ravagan 1 teach a hydroalcoholic gel formulation. One of skill in the art would not have recognized the need for this combination of components based on the claims of Ragavan 1. Therefore the claims of the present application are non-obvious over claims 1-15 and 31-33 of Ravagan 1.

U.S Patent No. 6,652,874 to Ragavan, et al. ("Ragavan 2")

Claims 1-5, 7 and 8 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 17 of U.S. Patent No. 6,652,874 to Ragavan ("Ragavan 2"). This rejection is improper based on a comparison of the pending claims, with claims 1-15 and 31-33 of the Ragavan 2 as shown below. Independent claim 1 of Ravagan 2 defines a drug formulation, comprising drug particles suitable for local or regional administration of an effective amount of the drug to provide relief from symptoms in a region in

patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically and wherein the drug is selected from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs.

The same comments and analysis apply as above. The claims of Ravagan 2 do not teach nor make obvious the combination of a hydroalcoholic gel with a penetration enhancer. It is the *combination* of the hydroalcoholic gel *and* a penetration enhancer that solublizes the drug and enhances flux of the drug through the skin. One of skill in the art would not have recognized the need for this combination of components based on the claims of Ragavan 2. Therefore the claims of the present application are non-obvious over claims 1-4 and 17 of Ravagan 2.

U.S. Patent No. 6,416,778 to Ragavan, et al. ("Ragavan 3")

The pending claims were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 12 of U.S. Patent No. 6,416,778 to Ragavan ("Ragavan 3") Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended. Independent claim 1 of Ravagan 3 defines a drug formulation comprising drug particles suitable for regional administration of an effective amount to provide relief from symptoms of a disease or disorder selected from the group consisting of endometriosis, endometrial bacterial infections, cancer, and endocrine conditions in a region in patients in need thereof, wherein the region is selected from the group consisting of the uterus, fallopian tubes, peritoneal space, pelvic cul-de-sac, ovaries, and urinogenital tract, wherein the effective amount is a dosage which results in low serum drug levels and reduced side effects as

compared to systemic administration of the drug, and wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam. Independent claim 12 defines a composition for treating endometriosis comprising particulate danazole in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug, when applied to the mucosal membranes of the female reproductive tract, wherein the carrier is selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam wherein the dosage of the danazole is effective to reduce the symptoms of endometriosis without causing blood levels of danazole achieved with systemic administration of the danazole.

The same comments and analysis apply as above. The claims of Ravagan 3 do not disclose nor make obvious the combination of a hydroalcoholic gel with a transdermal penetration enhancer. There is no mention of either element, much less any disclosure leading one to combine the two elements. One of skill in the art would not have recognized the need for this combination of components based on the claims of Ragavan 3. Therefore the claims of the present application are non-obvious over claims 1-4 and 17 of Ravagan 3.

Withdrawal of the nonstatutory double patenting rejection is respectfully solicited.

Rejoinder and allowance of all claims 1-5, 7, 8, 10-12, 14, 15, 17, and 19 is respectfully solicited.

Respectfully submitted,

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